REMARKS

Claims 25-28 are pending.

Claim 25 is amended to recite that the drug resistance gene is operably linked to the ubiquitin promoter; to replace reference to "targeting efficiency" with reference to "targeting number" and with reference to determining number(s) of targeted mouse ES cells in a cell colony; to refer to ES cell clones rather than ES cells, and to recite that the second targeting number is proportionately at least two-fold higher than the first targeting number.

The amendment to claim 25, subdivision (f), reciting that the second targeting number is "proportionately" at least two-fold higher than the first targeting number is supported, for example, in the specification at Table 2 on page 11, which indicates a "% Targeting" at column 6 for a variety of genes operably linked to the PGK or the ubiquitin promoter. The term "proportionately" is expressly supported because, as is known in the art, a percentage is a proportion (literally, "percent" is one part in a hundred), and also at the last line of paragraph [0030] on page 7, referring to a "ratio" (e.g., a comparison reflecting a quotient) of targeted to total drug resistant clones.

Support for the phrase "ES cell clones" is provided by column headings 4 and 5 in Table 2 as filed.

Support for use of the phrase "number of targeted mouse ES cell clones" can be found, for example, at paragraph [0029] of the specification as filed, and in Table 2 at columns 4-5 which indicate numbers of clones screened and numbers of colonies screened.

Support for the phrase "targeting number" with respect to genes operably linked to a PGK promoter or a ubiquitin promoter is presented in Table 2, column 5, headed "Targeted Clones."

The amendments to claim 25 are thus supported by the specification as filed and add no new matter.

Applicants submit that the amendments to claim 25 place the application in condition for allowance, and respectfully request entry of the amendments and allowance of the application.

Rejections Under 35 USC § 112, First Paragraph: Enablement

The Examiner rejected claims 25-28 as not enabled. The Examiner indicated that the specification is enabling for a method of determining targeting frequency of a targeting construct

in mouse embryonic stem (ES) cells, comprising: (a) construction a first targeting vector directed to a specific chromosomal location in a mouse ES cell, wherein the first targeting vector comprises a drug resistance gene operably linked to a PGK promoter; (b) introducing the first targeting vector into mouse ES cells in vitro to obtain a first group of targeted mouse ES cells; (c) determining the number of targeted mouse ES cells in a cell colony as measured by targeted gene modifications due to targeted, non-random insertions of the first targeting vector in the first group of targeted mouse ES cells; (d) constructing a second targeting vector directed to the specific chromosomal location of step (a), wherein the second targeting vector comprises a drug resistance gene operably linked to a ubiquitin promoter; (e) introducing the second targeting vector into a second group of mouse ES cells in vitro to obtain a second group of targeted mouse ES cells; and, (f) determining a second number of targeted mouse ES cells in a cell colony as measured by targeted gene modifications due to targeted, non-random insertions of the second targeting vector in the second group of targeted mouse ES cells, wherein the second targeting number is at least two-fold higher than the first targeting number.

Applicants have amended claim 25 to include the subject matter that the Examiner deemed enabled, and to refer to mouse ES cell clones. Claim 25 is also amended to indicate that the second targeting number is proportionately at least two-fold higher, to reflect the practical aspects of screening known to those skilled in the art, i.e., that the fold-increase in targeting number is generated from testing a sample or ratio or percentage or proportion (e.g., 100 ES cells) of targeted ES cells of a larger a group (e.g., a thousand or more ES cells) of ES cells. Accordingly, Applicants submit that the rejection is moot and the application is in condition for allowance.

Conclusion

It is believed that this document is fully responsive to the Final Office action dated 04 August 2008, and that the claim amendments herein place the application in condition for allowance.

Fees

Applicants submit that no fee is due in connection with this filing. If any fees are due, or overpayment has been made, please charge, or credit, Deposit Account No. 18-0650 in the amount of the overpayment or fee deficiency.

Respectfully submitted,

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